Risk assessment for metalworking fluids and cancer outcomes

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Abstract

Background—Metalworking fluids (MWF) are complex mixtures with dermal and inhalation exposure. Published reports reveal excess cancer risk.

Methods—Using published findings exposure response was derived for each attributable cancer site. Aggregate excess lifetime risk was estimated by applying a lifetable calculation.

Results—Cancer sites contributing the most attributable cases were larynx, esophagus, brain, female breast, and uterine cervix. With constant workplace MWF exposure of 0.1 mg/m^3 over a 45 years working life, the risk of attributable cancer was 3.7% or, excluding the less certain female cancers, 3.1%.

Conclusion—Substantial cancer risks occurred at 0.1 mg/m^3 MWF, one fourth of the current NIOSH recommended exposure limit for MWF total particulate. Because ingredients in current MWF remain from earlier formulations, it is likely that some MWF carcinogenicity persists today.

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AUTHORS' CONTRIBUTION

R MP participated in: a) conception or design of the work; b) the acquisition, analysis, or interpretation of data for the work; c) drafting the work or revising it critically for important intellectual content; d) final approval of the version to be published; and e) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICS APPROVAL AND INFORMED CONSENT

This work was based entirely on published, aggregate findings from investigations declaring compliance with institutional review boards.

DISCLOSURE (AUTHOR)

The author declares no conflicts of interest.

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DISCLAIMER

The findings and conclusions in this report are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Although important changes have occurred, newer agents are being continually introduced with little or no knowledge of chronic health risks.

Keywords

auto workers; esophageal cancer; excess lifetime risk; exposure response; laryngeal cancer

1 | INTRODUCTION

Metalworking fluids (MWF) are mixtures that vary widely across process categories (milling, turning, grinding, stamping, etc.), within manufacturing facilities, across enterprises and over time, with continually evolving constituents. The routes of exposure are dermal, to the bulk liquid phase from parts handling and MWF splash and mist, and by inhalation of dusts, mists, and vapors. The health effects of MWF exposures have been reviewed extensively.[1–5] The International Agency for Research on Cancer (IARC) has not yet assessed cancer risk from exposure to metalworking fluids as a group or an exposure circumstance (https://monographs.iarc.fr/ENG/Publications/internrep/14-002.pdf). IARC considers such an assessment of medium priority for monographs during 2015–2019. Potential carcinogens in MWF include hydrocarbons, chlorinated paraffins, aliphatic amines, nitrosamines, PAHs, formaldehyde-releasing agents, diethanolamine, and many other specialty additives. Bioassays of two water miscible MWF found evidence for carcinogenicity (http://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2016/february/tr591_peerdraft.pdf https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2014/may/draft_tr586_508.pdf). Respiratory disorders and performance deficits are the other major category of MWF health effects, observed as increased morbidity and mortality from nonmalignant respiratory disease, or reduced pulmonary function test results, as well as specific and potentially life-threatening immune-mediated disorders: adult-onset asthma and hypersensitivity pneumonitis (HP).[6,7] MWF in the manufacturing environment provide rich media for microbial proliferation, sustaining a wide diversity of organisms in the bacterial, mold, fungal, and other orders.

During the observational studies discussed here, over 800 000 workers in the United state were estimated to be routinely exposed to MWF in manufacturing and maintenance activities (most recent NIOSH assessment).[8] The exposures typically arise because MWF are applied as spray or liquid stream to the surfaces where metal cutting or other process activities occur for the purposes of lubrication, cooling, and removal of chips or other cutting debris.[9] MWF systems exist in a range from large central systems with sumps containing many tens of thousands of gallons of MWF, servicing dozens of operations, to small self-contained systems dedicated to a single machine. Operation of MWF systems includes filtration steps, tramp oil separation, and continual monitoring and adjustment of operating parameters such as pH, biocide levels, and lubricity.[10] There are four general classes of MWF: straight oils, soluble oils, synthetic, and semi-synthetic.[11] In this risk assessment, all types were treated as one generic entity because: a) there is wide diversity within those categories and b) in many operations environmental conditions are the result of multiple contributing sources of MWF. There is substantial overlap in ingredients: soluble

oils and semi-synthetics (but not synthetics) contain straight oils as components, while synthetics share ingredients with soluble oils and semi-synthetics (but not straight oils).

The challenge for risk assessment is to generalize from findings in the specific worker populations that have been observed over several prior decades, as well as from animal studies usually limited to a few priority components of MWF. The patterns of association vary across the populations studied both in the hazard identification phase of MWF investigations and in subsequent studies designed specifically to estimate exposure-response. In this risk assessment the goal is to describe attributable aggregate cancer risks associated with generic MWF exposure conditions, based on human studies.

2 | METHODS

2.1 | Compilation of mortality findings

The first step identified cancer sites with statistically significant excesses in MWF-exposed populations based on published reviews.[1,4,5] The studies contributing to this hazard identification step generally had insufficient retrospective exposure assessments to support a quantitative risk assessment; the reported associations were typically with duration in metalworking process classifications or with other broad generic categories. Because of the complex and changing compositions of MWF exposures, only gravimetric measures of the total mass of airborne dusts or mist exposures to any MWF are considered for risk assessment purposes, in some cases with restriction to the thoracic fraction.

In the second step, relative risk estimates for the specific cancer sites selected were obtained from published analyzes of mortality in a single cohort of workers drawn from three automobile manufacturing plants with diverse MWF exposures.[12] For this unique cohort an extensive retrospective exposure assessment had been performed and a detailed work history compiled on over 46 000 auto workers followed from 1941 through 1994.[13] Although all types of metalworking fluids were used in these plants soluble oils would have been the dominant exposure. This work was jointly funded by General Motors Corporation and the United Auto Workers union. The investigators selected the facilities for study without prior knowledge of cancer excesses there. The cancer sites included in the risk assessment and the publications providing exposure-response estimates are displayed in Table 1.[12,14–24] All these studies were based on the GM-UAW cohort of Eisen et al.[12] Also included in the cancer risk assessment were the MWF associations with cervical and breast cancer, first observed in this autoworker study which included a large female workforce.[20] Support for a breast cancer association with MWF was previously reported in a large population-based case-control study.[25] Some of the reported results duplicate earlier analyzes of this cohort; only the later or more detailed analyzes were used. The MWF associations for colon cancer and bladder cancer lacked sufficient certainty in the prior literature to be included. All risk estimates from the three auto plants for the cancer sites previously identified in the published literature as MWF-associated were included in the risk assessment regardless of value or statistical significance in the three UAW-GM auto plants, as is appropriate for a meta-analysis with strong prior evidence of causal associations. In analyzes stratified on exposure levels, restricting to significant exposure response would bias the summary risk estimates upward.

2.2 | Analysis

The contributing analyzes utilized different designs and analytical methods (see Supplementary Table S1). The diverse reported measures of association were transformed into a single, common measure of relative rate (RR) equivalent to a simple linear association, RR = 1 + b × cumX, from which excess relative rate (ERR) = b × cumX, and the exposure response (XR) = ERR/cumX = b, were derived. This step depended on the modeling specification scenario of which there were three (Table 2).

In the third step, combining results from the various studies, categorical, and spline analyzes often produced several final estimates for the same exposure-response. For each specific outcome, these were combined as a weighted average, the weights applied being $(\beta/SE_\beta)^2$. All strata for which a mean cumulative exposure could be assigned were used. If the stratum mean was not reported, the geometric mean of the stratum limits was used. If the lowest stratum merely had an upper limit or the upper stratum had no upper limit, the stratum estimate was not used. Similarly, when analyzes focused on specific types of MWF, example straight, soluble, etc., each of these estimates was included in the outcome-specific average exposure response using the same weighting procedure (see Supplementary Table S1), recognizing that some of these MWF-specific estimates were probably confounded by exposures to other types of MWF. When SE_β was not reported, it was derived from the lower confidence limit.

Using the life-table approach as implemented in the BEIR IV report,[26] which accounts for competing risks for the onset of a discrete outcome, together with estimates of exposure-response for the individual cancer sites, one can estimate the excess numbers of cancer deaths that would occur as a result of lifetime exposures at various concentrations, that is the excess lifetime risk (XLTR). In this calculation, cumulative exposure is derived from the fixed exposure intensity and increasing age (in some analyzes with a lag). This method assumes irreversibility of risk and removes predicted exposure-attributable deaths from the population at risk with increasing age along with deaths arising from the usual causes in the general population. Using a national life-table constructed from Social Security data[27] the surviving population was calculated annually through age 85 for each specified exposure level assuming work-related exposure starts at age 20 and ceases at age 65 for a 45 years exposure. The number of MWF-associated deaths in each age year was calculated by multiplying the surviving population (SrvPop) by the hypothetical cumulative exposure at the attained age and by the sum of the products of: a) the site-specific average exposure-response estimates (b(i); Table 3), and b) the corresponding age- and site-specific national death rates[28] (assuming equal proportions by sex and a 10% nonwhite population):

$$\text{excess deaths} = \text{SrvPop} \times \text{cum(MWF)} \times \sum_{i=1}^{n}\{\text{b(i)} \times \text{rate(i, age)}\}$$

For female premenopausal breast cancer,[20] the cumulative exposure metric was based on the prior 10 years of exposure (unlagged) as specified in the regression analysis and the background rate was adjusted to account for both incident ($n = 46$) and fatal ($n = 64$) cases up to age 51, as in the reported regression analysis.

Thus it was assumed that the risks at different cancer sites were acting independently and could be summed based on the observed individual cancer site estimates. Different contributing studies used various lag periods to address latency in estimating exposure response with the majority of estimates actually calculated without a presumed lag period (eg, Eisen et al[12]). Therefore in the calculation of XLTR, lag periods of 20, 10, and 0 years were applied for comparison.

3 | RESULTS

The predicted attributable cancer deaths (assuming 10 years lag) totaled 0.48 per thousand person-year at age 60 after 40 years of work with 1.0 mg/m^3-year MWF cumulative exposure, corresponding to 40–10 = 30 years at 0.033 mg/m^3 MWF (Table 3); the premenopausal breast cancer contribution was calculated for age 50. The cancer sites with the highest estimated rates of attributable cases were for larynx with 0.18 per 1000 person-year (at 1.0 mg/m^3-year MWF) and esophagus with 0.12 per 1000 person-year followed by brain (0.05 per 1000) and, in women, cervix (0.05 per 1000), and breast cancer (0.04 per 1000), (Table 3), but the estimates for the female cancer sites were based on many fewer person-years of observation[12] and there was less prior evidence of MWF-associated risk for those cancer sites. Excess lifetime risk of cancer mortality attributable to MWF was calculated (Table 4; see Supplementary Table S2 for example of life-table calculation). With three assumed lag periods modest differences resulted. At a constant working life exposure level of 0.1 mg/m^3 MWF and a 10 year lag, the XLTR was approximately 3.7 percent (37 per 1000), and at 0.02 mg/m^3 it was 0.7 percent (7 per 1000). Excluding the female cancer sites for which there was less supporting evidence, and with a 10 year lag, the XLTR at 0.1 mg/m^3 MWF was approximately 3.1 percent (31 per 1000), and at 0.02 mg/m^3 it was 0.6 percent (6 per 1000) (Table 4).

4 | DISCUSSION

At 0.1 mg/m^3 concentrations of the MWF typically in use in the latter half of the 20th Century, that is at one fourth of the current NIOSH Recommended Exposure Limit (REL), this study suggests that substantial excess lifetime risks of fatal malignant disease (greater than 3 percent) remain. The primary affected cancer sites are in the upper and lower digestive tract. Lung cancer risks, observed to be generally small, have been hypothesized to reflect a protective role of endotoxin exposures generated by water-based MWF.[22] Based on this risk assessment, cancer mortality is a candidate for the critical effect in a comprehensive risk assessment for MWF, as are respiratory impairment, incident asthma, and hypersensitivity pneumonitis, for which separate risk assessments have been conducted.

4.1 | Limitations

Although only three automotive manufacturing plants with MWF exposures were studied for cancer mortality, these three large plants (including transmission, gear and axle, steering gear, and related operations) over a period of more than 50 years produced thousands of specific parts on machine tools serviced by hundreds of central MWF sumps containing specific fluid types and ingredients considered optimal for those applications. The fluid formulations were those available from numerous vendors serving the entire metalworking

industry, not just automotive. The period of observation sampled all these systems and the resulting estimates of relative risk represent an average effect over this entire manufacturing experience. These observations should be generalizable to most large scale ferrous and aluminum metalworking manufacturing during that period but may not represent as well smaller machining operations often without central coolant systems. On the other hand, the plants studied had relatively little cast iron machining and grinding compared to, for example engine plants or bearing plants where stomach cancer excesses have been observed. [1,3,29] No stomach cancer excess was observed in the Eisen study[12] used for this risk assessment.

There are multiple limitations in these estimates of XLTR of cancer mortality beyond the uncertainties of historical MWF exposure composition. All of the non-spline reported statistical models using continuous exposure metrics in the estimation of exposure response utilized a log-linear model form which would tend to underestimate the magnitude of the association in the mid-range of the exposure variable, which is what was used in deriving a common linear exposure response metric. Although different MWF would confer different levels of cancer mortality risk, the estimates produced here were from the generic mix of MWF over the periods of observation thus diluting the contributions of specific MWF formulations conferring high risk but enabling the aggregation of specific cancer-site estimates to produce an overall summary risk of cancer death. Predicted excess relative rates and attributable cases for the 13 specific cancer sites in some cases were based on quite uncertain estimates, but the aggregate effect of these statistically independent effects would be more stable. Personal risk factors such as smoking were not available in most analyzes but all were based on internal comparisons which would tend to reduce bias from those risk factors. For the leading cancer sites with deaths attributable to MWF (larynx, esophagus, brain but not lung), smoking is a relatively small risk factor. Moreover, smoking is a risk factor for poor health and relatively earlier termination of employment and, thus, it would contribute to a healthy worker survivor bias and likely negative confounding of analyzes of exposure response related to cumulative exposure.

5 | CONCLUSION

Because many ingredients in current MWF remain from earlier formulations, it is reasonable to assume that some MWF carcinogenicity persists today. Although some important changes have occurred, such as elimination of acid-refined oils many years ago and reduction of nitrosamine-forming chemicals, newer agents are being continually introduced with little or no knowledge of associated chronic health risks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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TABLE 1

Cancer sites included in risk assessment based on UAW/ General Motors study of MWF (Eisen et al 2001[12])

Cancer site	References
Esophagus	Sullivan et al 1998[16]
Stomach	Eisen et al 2001[12]
Rectum	Eisen et al 2001[12]; Malloy et al 2007[21]
Pancreas	Bardin et al 1997[15]
Biliary tract	Bardin et al. 2005[19]
Larynx	Eisen et al 1994[14]
Lung	Mehta et al 2010[22]
Melanoma	Costello et al 2011[23]
Breast	Thompson et al 2005[20]
Cervical	Betenia et al 2012[24]
Prostate	Agalliu et al 2005[18]
Brain	Eisen et al 2001[12]; Thurston et al 2002[17]
Lymphopoietic	Eisen et al 2001[12]

TABLE 2

Transformation of association measures to equivalent linear form

scen	Original model form in published study	Linearized exposure response, b from RR = 1 + b × cumX: b = (RR–1)/cumX
1	Loglinear logistic or Poisson regression, on continuous cumulative exposure	Evaluate OR @ mean cumX (mg/m^3-year) via inverse log transformation; linearize and express exposure response as ERR per mg/m^3-year MWF: $b=(\exp(\beta \times \mathrm{cumX_{mean}})-1)/\mathrm{cumX_{mean}}$
2	Proportional hazard regression, spline, on continuous cumulative exposure	Apply reported HR @ investigator-specified cumulative exposures; linearize and express XR as ERR per mg/m^3-year MWF: $b=(\mathrm{HR}-1)/\mathrm{cumX_{spec}}$
3	Loglinear logistic or Poisson regression, on categorical strata of cumulative exposure	linearize OR @ stratum and express XR as ERR per mg/m^3-year MWF: $b=(\exp(\beta)-1)/\mathrm{cumX_{start}}$

scen, scenario; RR, relative risk; OR, odds ratio; β, reported parameter estimate; HR, hazard ratio; ERR, excess relative risk.

TABLE 3

Estimated exposure response and attributable deaths for specific cancer site outcomes

Cancer site	Exposure response (b)[a]	Attributable proportion[a]	Attributable deaths per 1000 *P*-year[a,b]
Esophagus	0.596	0.373	0.117
Stomach	−0.091	−0.101	−0.017
Rectum	0.135	0.119	0.015
Pancreas	0.014	0.014	0.004
Liver/bile duct	0.105	0.095	0.005
Larynx	1.994	0.666	0.179
Lung	0.008	0.008	0.022
Skin/melanoma	0.120	0.107	0.016
Breast (women)[c]	0.083	0.076	0.039
Cervix (women)	1.281	0.562	0.045
Prostate (men)	0.008	0.008	0.001
Brain	0.298	0.229	0.051
Lymphoid leukemia	0.005	0.005	0.000
Total	-	-	0.477

[a] ERR per 1.0 mg/m^3-year of MWF cumulative exposure; attributable proportion = ERR/(1 + ERR).

[b] At age 60; with 10 year lag, 1.0 mg/m^3-year cumulative exposure corresponds to 40 years at 1.0/(40–10) = 0.033 mg/m^3 MWF constant exposure; assumes equal proportions of men and women.

[c] For breast cancer at age 50, for 1.0 mg/m^3-year cumulative exposure based on 10-year exposure window (corresponding to 10 years at 0.1 mg/m^3 MWF) and risk for premenopausal cancer (age < 52) (Thompson et al 2005).[20]

TABLE 4

Excess lifetime risk for cancer mortality attributable to metalworking fluid exposures, by lag period applied (per 1000)

MWF	cumX[a]	Excess lifetime risk/1000 lag period, year				
mg/m³	mg/m³-year	20	10	10[b]	0	
0.5	22.5	131	167	141	190	
0.2	9.00	55	71	60	82	
0.1	4.50	28	37	31	42	
0.05	2.25	14	19	15	21	
0.02	0.90	6	7	6	9	
0.01	0.45	3	4	3	4	
0.005	0.23	1.4	1.9	1.6	2.2	
0.002	0.09	0.6	0.7	0.6	0.9	
0.001	0.05	0	0.4	0.3	0.4	

[a]Cumulative exposure with 45 year working career.

[b]Excluding female cancers.